DECLARATION

I, Toshiyuki Ueno, a member of Yokogawa Electric Corporation (Yokogawa Denki Kabushiki Gaisha) having a principal place of business at 9-32, Nakacho 2-chome, Musashino-shi, Tokyo 180-8750 Japan, do solemnly declare that the attached documents are full, true and faithful translation made by me this 30th day of June 2008 of a certified copy of the Japanese Patent Application No. 1999-149399 "Biochip Reader" consisting of Application for certificate dully certified thereon and Specification. And I make this solemn declaration conscientiously believing the same to be true.

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[Document Name] Specification

[Title of the Invention] Biochip Reader

[What Is Claimed Is]

[Claim 1]

A biochip reader for reading image data according to a plurality of samples using an optical detector by irradiating light at a biochip whereupon said plurality of samples are arranged in spots or arrays, comprising means for arranging multiple pieces of spectroscopic information of the sample under analysis in spaces among said images.

[Claim 2]

A biochip reader as defined in claim 1, wherein said means comprises a grating, a combination of an optical filter and optical shift means, or a Fourier spectrometer, arranged between said samples and said optical detector.

[Claim 3]

A biochip reader as defined in claim 1, wherein said means is configured so that spectroscopic information is developed on said optical

detector in a two-dimensional manner if said samples are arranged in spots.

[Claim 4]

A biochip reader as defined in claim 1, wherein said means is a scanning confocal microscope, a non-scanning confocal microscope, or a dual-grating excitation microscope.

[Claim 5]

A biochip reader as defined in claim 1, comprising means for separating signals of said spectroscopic information from noise by using known spectra and a regression method.

[Claim 6]

A biochip reader as defined in claim 1, wherein an aperture for restricting the area of spectroscopy is aligned with the position of each sample or with part of each sample.

[Claim 7]

A biochip reader for reading image data according to a plurality of samples using an optical detector by irradiating light at a biochip whereupon said plurality of samples are arranged in spots or arrays, wherein reading means is a non-scanning confocal microscope having an aperture positioned to be optically conjugate with the position of the image of said sample or part of said sample.

[Detailed Description of the Invention]

[0001]

[Technical Field to Which the Invention Pertains]

The present invention relates to a reader for reading the wavelengths of fluorescence caused by marking such samples as deoxyribonucleic acid (DNA) or protein with a fluorescent substance and then exciting the substance by laser light or other alternative means. More specifically, the invention relates to improvements made in order to reduce the size and cost of the reader and increase the accuracy thereof.

[0002]

[Description of the Prior Art]

The prior art discloses a technique in which deoxyribonucleic acid (DNA) or protein is marked with a fluorescent substance, the substance is excited by irradiation with laser light, and the resulting wavelengths of fluorescence are read so that DNA or protein is detected and analyzed. In this technique, a biochip onto which samples of DNA or protein marked with the fluorescent substance are spotted in arrays is used.

[0003]

The biochip is read by irradiating and scanning laser light laterally, for example, to excite spots of the fluorescent substance arranged in arrays. The emitted fluorescent light is then condensed by an optical fiber, for example, and received by an optical detector through an optical filter to detect the desired wavelength. When reading of one line (or

array) of spots is completed, the biochip is moved longitudinally to repeat the same process as described above. This process is repeated until the biochip is read entirely.

[0004]

[Problems to Be Solved by the Invention]

Such a conventional biochip reader as discussed above has had the following problems, however:

1) The biochip has too many spots, is too large in terms of outside dimensions, and has too many arrays.

2) Fluorescence wavelengths are separated by means of an optical filter. It is therefore difficult to separate the wavelengths of polychrome fluorescent light since its spectra mix with each other depending on the concentration of each color.

3) The quantitativeness of measurement deteriorates due to the mixing of fluorescent light with self-emissions, background light or the like. This results in decreased accuracy.

4) A prolonged period of time is required when switching between optical filters and between optical detectors according to the fluorescence color.

5) Although the biochip reader can be speeded up by arranging multiple optical filters and optical detectors and letting the optical detector receive fluorescent light at the same time instead of switching between the filters and between the optical detectors, this approach has the problem of increased cost.

6) Using a scanning confocal microscope with the biochip reader increases

the number of system components. This results in an increase in the system's cost and size, as well as a longer time to perform measurement.

[0005]

The object of the present invention is to solve the aforementioned problems by providing a biochip reader which can simultaneously achieve three objectives: downsizing, cost reduction and accuracy improvement.

[0006]

[Means for Solving Problems]

In order to achieve the aforementioned object, the present invention provides a biochip reader according to claim 1, wherein light is irradiated at a biochip onto which multiple samples are arranged in spots or in linear arrays and image data according to the multiple samples is read using an optical detector. The biochip reader comprises means for arranging multiple pieces of spectroscopic information on the sample under analysis in spaces between the images of the aforementioned samples.

[0007]

According to the biochip reader configured in such a way as described above, it is possible to output pieces of spectroscopic information on the samples into spaces between the images of the samples and thereby realize simultaneous, multi-wavelength measurement easily. According to this configuration, it is also possible to acquire multi-wavelength information using a compact biochip reader.

[0008]

According to claim 2, the aforementioned means can be realized by

arranging a grating, a combination of an optical filter and optical shift means, or a Fourier spectrometer between the samples and the optical detector. Thus, it is possible to use one of these configurations as necessary.

[0009]

According to claim 3, it is also possible to develop spectroscopic information on the optical detector in a two-dimensional manner if the samples are arranged in spots. According to this feature of the present invention, it is possible to perform measurement that provides large amounts of information and is precise while the biochip reader is relatively compact.

[0010]

According to claim 4, either a scanning confocal microscope, a non-scanning confocal microscope, or a dual-grating excitation microscope can be used as appropriate.

[0011]

According to claim 5, it is possible to increase the accuracy of measurement by employing means for separating signals of spectroscopic information from noise using known spectra and a regression method.

[0012]

According to claim 6, an aperture for restricting the area of spectroscopy can be aligned with the position of each sample or with part of each sample to acquire spectroscopic information with reduced noise.

[0013]

According to claim 7, the biochip reader comprises, as reading means, a

non-scanning confocal microscope having an aperture positioned to be optically conjugate with the position of the image of the sample or of part thereof. This configuration also allows for easy acquisition of spectroscopic information with reduced noise.

[0014]

[Mode for Carrying out the Invention]

The present invention is described in detail below with reference to the accompanying drawings. FIG. 1 is a schematic block diagram showing one embodiment of a biochip reader in accordance with the present invention.

In FIG. 1, the numeral 1 indicates a light source for emitting laser light, the numeral 2 indicates a lens for making parallel the laser light emitted by the light source 1, the numeral 3 indicates a dichroic mirror, the numeral 4 indicates an objective lens, the numeral 5 indicates a sample, the numeral 6 indicates a grating, the numeral 7 indicates a lens, and the numeral 8 indicates an optical detector.

[0015]

Light (excitation light) emitted by the light source 1 is made parallel by the lens 2, is reflected by the dichroic mirror 3, is condensed through the objective lens 4, and is irradiated at the sample 5. This irradiation causes the sample 5 to emit fluorescent light (whose wavelength differs from that of the excitation light). The fluorescent light then retraces the path that the excitation light followed, by passing through the objective lens 4 and reaching the dichroic mirror 3.

[0016]

The fluorescent light that was emitted from the sample 5 and transmitted through the dichroic mirror 3 diffracts at the grating 6. The diffraction angle of the fluorescent light is relative to its wavelength. The fluorescent light thus diffracted by the grating 6 is condensed onto the optical detector 8 through the lens 7. As the optical detector 8, a camera is used, for example.

[0017]

If, for example, spots of four samples S1 to S4 are arranged on a biochip as shown in FIG. 2, spectroscopic images (spectra) with wavelengths of $\lambda 1$ to λn are formed for these respective samples in spatially different positions on the optical detector 8, as shown in FIG. 3. These spectroscopic images are spectroscopic information and can well be measured with a monochrome camera. As is evident from the figures, gaps between the spots are skillfully used in this example.

[0018]

Although the embodiment described above is based on a biochip on which spots are placed sporadically in arrays, the present invention is not limited to this sample arrangement. The invention can also be applied to fluorescence patterns of electrophoresis arranged in linear arrays. In this case, images shown in FIG. 4 are obtained. That is, spectroscopic images with wavelengths of $\lambda 1$ to λn are formed for the electrophoresis pattern of each lane (along the longitudinal axis) in spatially different positions along the lateral axis.

[0019]

FIG. 5 is a schematic block diagram showing another embodiment of the

present invention. In the embodiment of FIG. 5, two gratings are arranged so that their directions of diffraction are at right angles to each other. According to this configuration, two-dimensional spectra are obtained as shown in FIG. 6. If, for example, the spectral pattern is graduated in 100-nm increments laterally (X-axis direction) and in 10-nm increments longitudinally (Y-axis direction), it is possible to perform measurement with a wider dynamic range and higher precision.

[0020]

FIG. 7 shows an embodiment in which dichroic mirrors are used in place of the gratings. These dichroic mirrors are combinations of optical filters with optical shift means. As shown in FIG. 7, dichroic mirrors (optical filters) 31, 32 and 33 with different transmission wavelengths are stacked on the optical axis. In this embodiment, the angle of each dichroic mirror is determined so that light is reflected by the dichroic mirror at the same angle as it diffracts at a grating (equivalent to the optical shift means).

[0021]

FIG. 8 is an embodiment in which a non-moving Fourier spectrometer 81, such as a Savart or a Michelson model, is used in place of the gratings or dichroic mirrors. In this embodiment, images formed at the optical detector 8 are not spectra themselves but an image of interference fringes. Consequently, spectra can be obtained by using computation means (not shown in the figure) and subjecting this image to a Fourier transform process.

[0022]

It should be noted that the measurement resolution can be further

improved by using a confocal microscope or a dual-grating microscope instead of a regular fluorescence microscope or a camera. The quantitativeness of measurement is also improved because the slice effect of the confocal method makes it possible to always measure a constant volume of samples even if the thickness of each sample varies. In this embodiment, the confocal microscope may be of the non-scanning type.

[0023]

As shown in FIG. 9, such noise as self-emission whose wavelength slightly differs from that of the original fluorescent light can be removed easily because the properties of the reagent to be used are already known. If necessary, a signal spectrum may be separated using a regression method. With this approach, it is possible to easily achieve high precision and high sensitivity.

[0024]

For spectroscopy, it is necessary to restrict the area of measurement using a shield means, such as slits. For this reason, an aperture A is optically aligned with the area of a sample S1 or with part of the sample S1, for example, as shown in FIG. 10. This arrangement makes it possible to most effectively use the area.

[0025]

This arrangement is also effective for removing errors due to disorder in the edges of a sample. The shape of the aperture may not necessarily be circular; it may be rectangular instead.

[0026]

The aperture shown in FIG. 10 or the rectangular aperture described

above may be used as a pinhole or slit for a non-scanning confocal microscope. With this approach, it is possible for even a small and inexpensive microscope to achieve the high resolution characteristic of confocal microscopes and the quantitativeness due to the slice effect.

In this embodiment, the detection means is not limited to the spectroscopy method shown in FIG. 1, but may be a regular filter method.

[0027]

[Effect of the Invention]

As described above, the following advantages are offered in accordance with the present invention.

1) Multiple wavelengths of fluorescence can be measured simultaneously without having to change the filter and/or optical detector. It is therefore possible to realize a compact biochip reader.

2) A monochrome camera may be used to photograph spectra displayed on an optical detector for economical analysis.

3) Spectra displayed on an optical detector can be easily changed to two-dimensional spectra for higher precision.

[Brief Description of the Drawings]

[FIG. 1]

FIG. 1 is a schematic block diagram showing one embodiment of a biochip reader in accordance with the present invention.

[FIG. 2]

FIG. 2 is a schematic view showing an arrangement of samples on a biochip.

[FIG. 3]

FIG. 3 is a schematic view showing pieces of spectroscopic information indicated on an optical detector.

[FIG. 4]

FIG. 4 is a schematic view showing pieces of spectroscopic information provided when samples arranged in linear arrays are measured.

[FIG. 5]

FIG. 5 is a schematic block diagram showing another embodiment of the present invention.

[FIG. 6]

FIG. 6 is a schematic view showing spectroscopic images obtained when pieces of spectroscopic information are developed in a two-dimensional way.

[FIG. 7]

FIG. 7 is a schematic block diagram showing yet another embodiment of the present invention.

[FIG. 8]

FIG. 8 is a schematic block diagram showing still another embodiment of the present invention.

[FIG. 9]

FIG. 9 is a graph showing the distribution of self-emission, etc.

[FIG. 10]

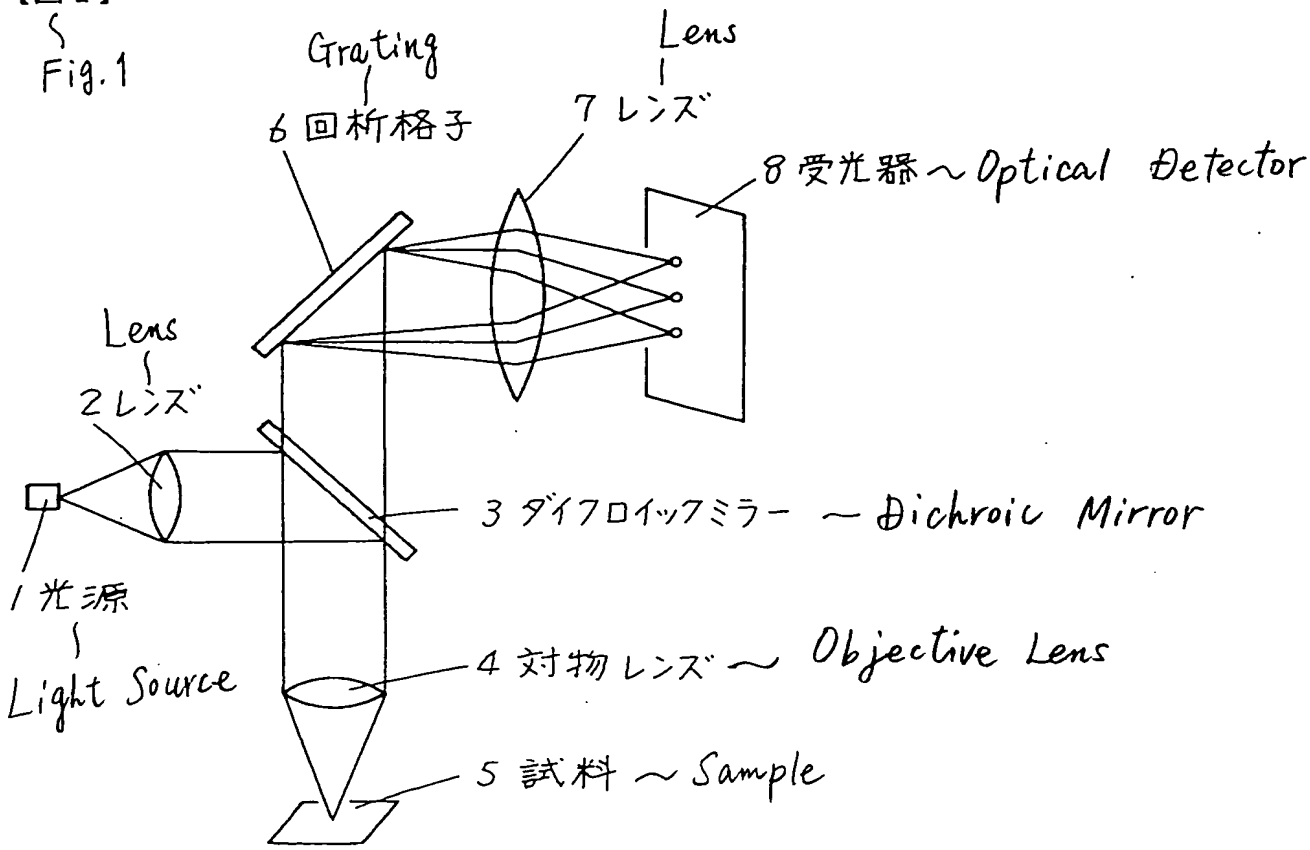
FIG. 10 is a schematic view showing the relationship between samples and apertures.

[Explanations of Letters or Numerals]

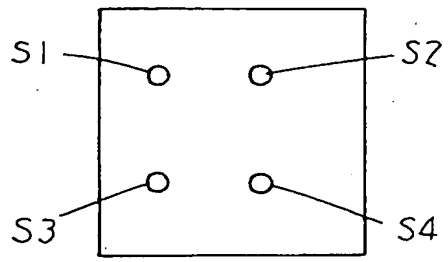
1	Light source
2	Lens
3, 31, 32, 33	Dichroic mirrors
4	Objective lens
5, S1, S2, S3, S4	Samples
6, 61	Gratings
7	Lens
8	Optical detector
81	Fourier spectrometer
A	Aperture

【書類名】　図面 — Drawings
Document Name

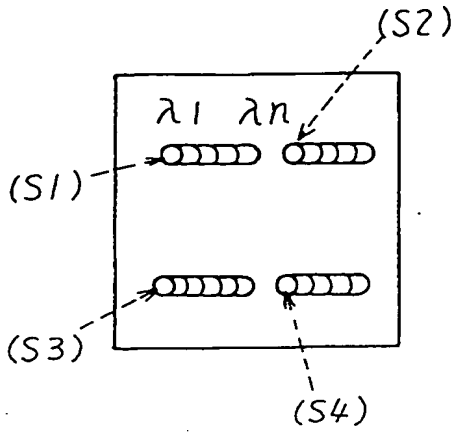
【図１】
Fig.1



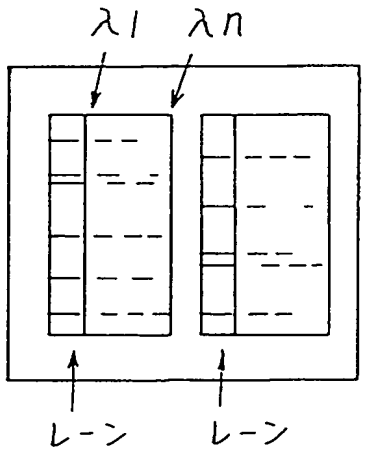
【図２】～ Fig. 2



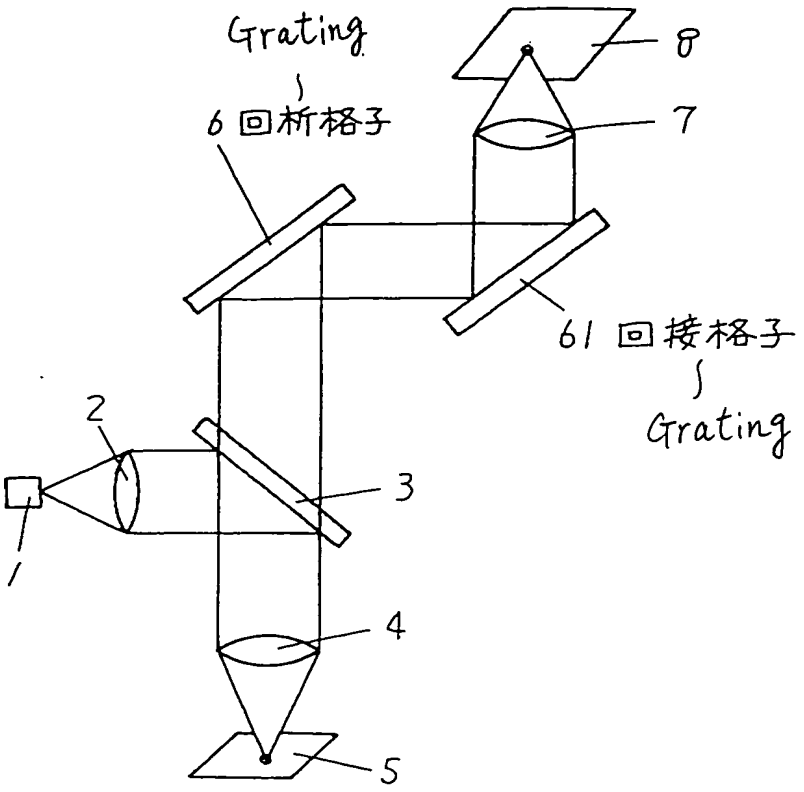
【図3】～ Fig. 3



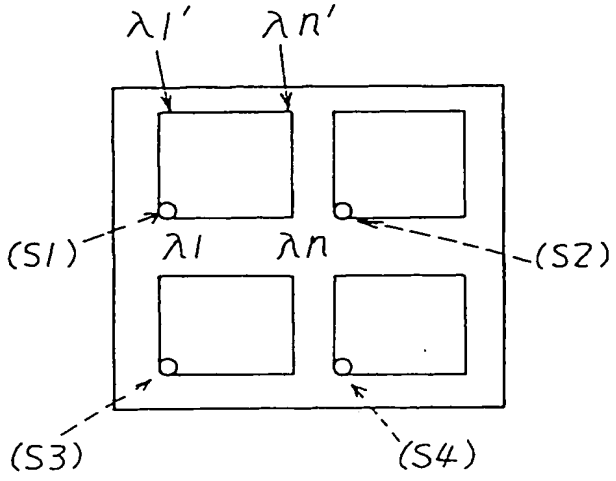
【図4】～ Fig. 4



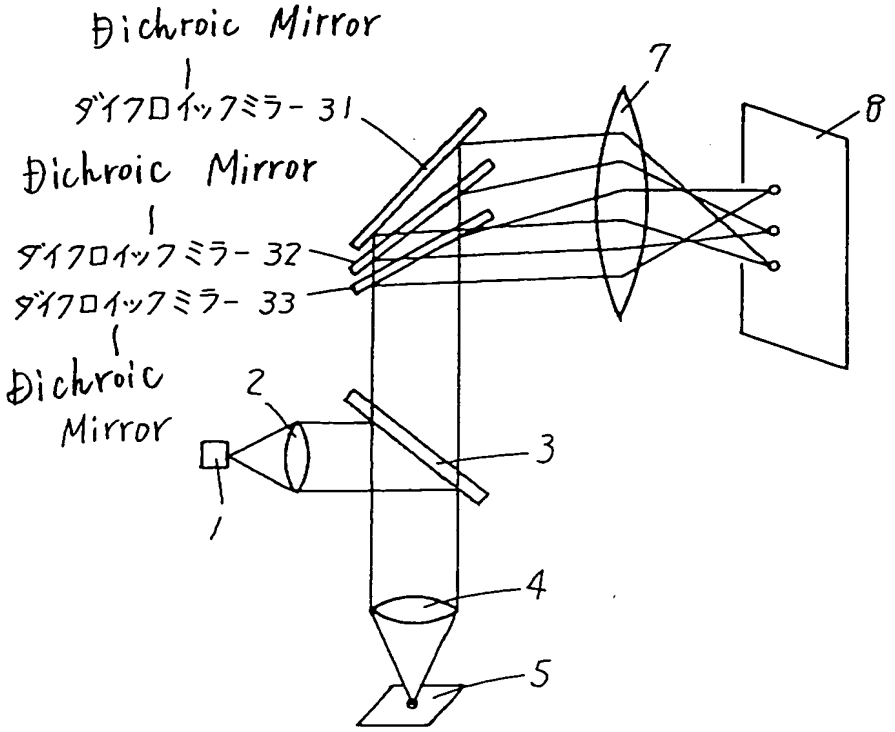
【図５】～Fig. 5



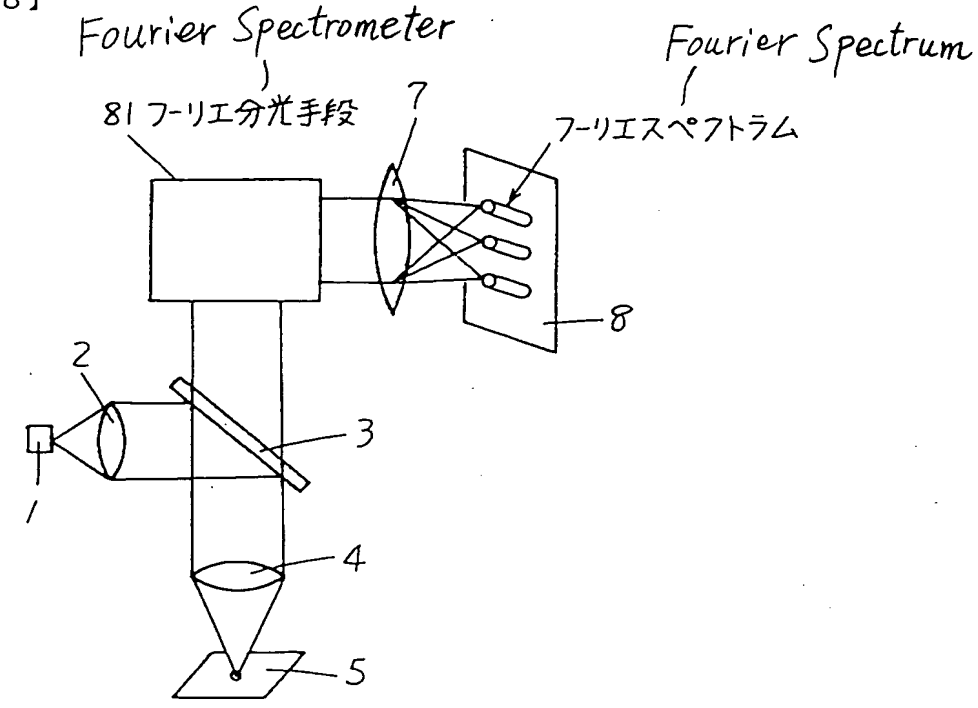
【図６】～Fig. 6



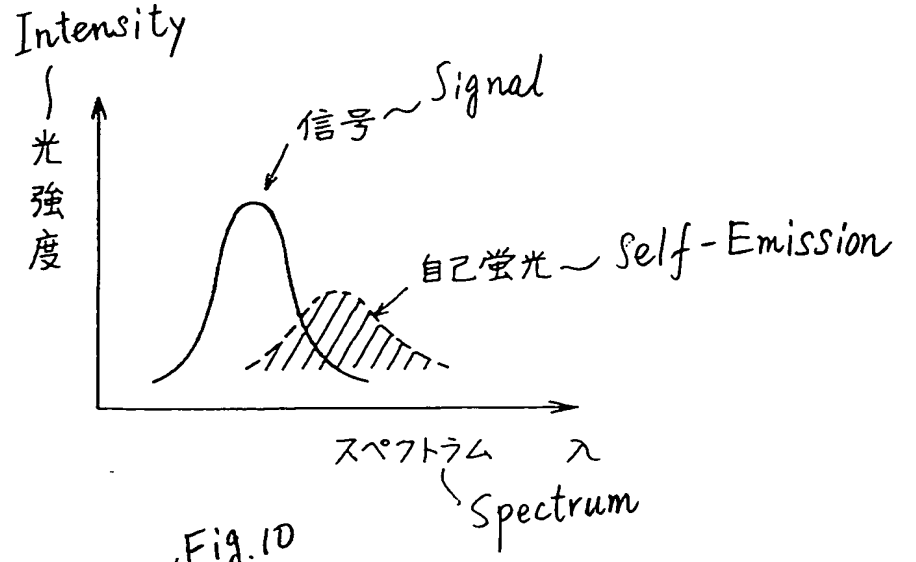
【図７】～Fig. 7



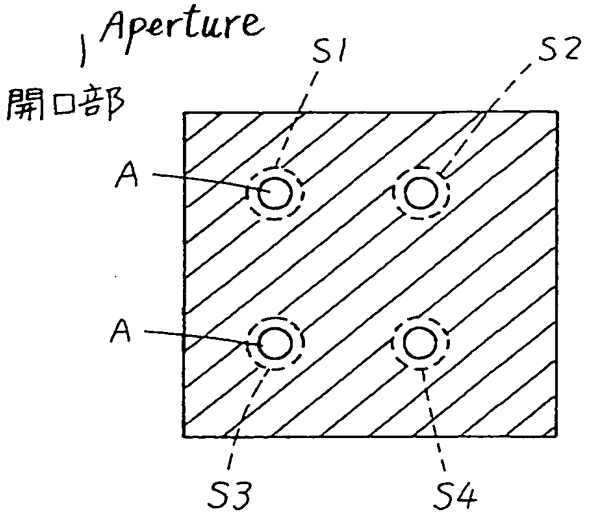
【図８】～Fig. 8



【図９】～Fig.9



【図１０】～Fig.10



[Document Name] Abstract

[Abstract]

[Object of the Invention]

The object of the present invention is to provide a biochip reader which can simultaneously achieve three objectives: downsizing, cost reduction and accuracy improvement.

[Means for Solving Problems]

A biochip reader, wherein light is irradiated at a biochip on which multiple samples are arranged in spots or in linear arrays and image data according to the multiple samples is read using an optical detector. The biochip reader comprises means for arranging multiple pieces of spectroscopic information on the sample under analysis in spaces between the images of the aforementioned samples.

[Chosen Drawing] FIG. 1